UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA

THE CITY OF HUNTINGTON, Plaintiff, v. AMERISOUCEBERGEN DRUG CORPORATION, *et al.*, Defendants.	Civil Action No. 3:17-01362
CABELL COUNTY COMMISSION, Plaintiff, v. AMERISOUCEBERGEN DRUG CORPORATION, *et al.*, Defendants.	

PLAINTIFFS' PROPOSED SURREPLY IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE CERTAIN EXPERT TESTIMONY OF KATHERINE KEYES

December 1, 2020

Defendants' Reply raises several new issues, to which Plaintiffs here respond, but none of Defendants' arguments changes in any way that their motion to exclude is addressed to specific, discrete portions of Dr. Katherine Keyes' August 3, 2020 Report, Dkt. 1097-18, and does not affect the opinions she intends to offer or the vast majority of the explanation she has offered to support those opinions. Nor do Defendants' arguments provide any basis to exclude even the limited portions of Dr. Keyes' testimony to which they apply.

I. Dr. Keyes' Computation of Overdose Deaths Caused by Prescription Opioids

With respect to Dr. Keyes' computation of overdose deaths attributable to prescription opioids, Defendants make two new arguments, neither of which has merit. *First*, Defendants claim that the CDC's description of multiple ICD-10 codes "*involved*" in a death is different from a conclusion that each drug was a contributing *cause* of death. Reply Br. 4.[1] Defendants' argument is rebutted by the CDC's own website, which explicitly describes the ICD-10 codes as providing a format for reporting "causes of death on the death certificate," defines "underlying cause of death" and "nonunderlying causes of death," and further directs that "[t]he combination of underlying and nonunderlying causes *is the multiple causes of death*." [2] Accordingly, where a death certificate includes an ICD-10 code for a prescription opioid, CDC guidelines provide that the prescription opioid is a "cause of death," regardless of whether any other causes (e.g., illicit opioids) are also listed.

[1] "Reply Br." refers to Defendants' reply brief. Dkt. 1172. "Br. Opp." refers to Plaintiffs' brief in opposition to Defendants' motion to exclude. Dkt. 1160. "Br Supp." refers to Defendants' motion to exclude and brief in support. Dkt. 1056.

[2] *International Classification of Diseases, Tenth Revision (ICD-10)*, Centers for Disease Control and Prevention, https://www.cdc.gov/nchs/icd/icd10.htm (last visited Nov. 30, 2020) (emphasis added).

Second, Defendants claim that the testimony of West Virginia Chief Medical Officer, Alan Mock, M.D., contradicts Dr. Keyes' explanation of the causative role of prescription opioids in a multi-drug case. In fact Dr. Mock's testimony supports Dr. Keyes' view that every drug listed on a death certificate is properly viewed as a cause of death:

> In a combined intoxication of multiple opioids, then they're all significant. So in a combined intoxication between prescribed Oxycodone [sic] and illicitly-manufactured fentanyl, *both would be significant, and both would contribute to these numbers*.[3]

II. Dr. Keyes' Computation of OUD Cases

Defendants make four arguments with respect to Dr. Keyes' computation of OUD cases, but, again, none of these has merit. *First*, Defendants argue that Dr. Keyes overestimated the number of OUD cases in Cabell/Huntington because her methodology did not differentiate between fentanyl and its analogs, and did not take account of what they contend is the greater toxicity of the latter. Once again, the testimony of Dr. Mock contradicts Defendants' argument. That testimony establishes that there was no need for Dr. Keyes to take account of possible differences between fentanyl and its analogs because there was little to no carfentanil—the only fentanyl analog mentioned by the Defendants as having higher toxicity[4]—in Cabell County during the relevant period.[5] Because there is no factual support for Defendants' allegation that higher toxicity fentanyl analogs were present in Cabell/Huntington, there is no basis for Dr. Keyes to have considered them in her analysis.

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[3] Mock Dep. 253:7–12 (emphasis added), Ex. A.

[4] Defendants argue that Plaintiffs "conceded" the greater toxicity of fentanyl analogs, Reply Br. 10, which is false. Plaintiffs merely acknowledged the evidence, which Defendants seek to ignore, that some analogs such as carfentanil were *more* potent than fentanyl, while others were *less* potent than fentanyl. Br. Opp. 22 n.44.

[5] Mock Dep. 214:6–215:15, Ex. A.

Second, Defendants argue for the first time that multiplier methods cannot be used to estimate changes in prevalence over time because such analysis is "fundamentally incoherent." Reply Br. 8. Defendants continue to misread the authority on which they rely. Population stability is an "assumption" of several indirect measurement methods, the absence of which "may" introduce error.[6] But the text on which Defendants rely recognizes that a perfectly stable "closed population (i.e., no deaths, new cases, cessation or migration) is . . . an impossibility."[7] Nonetheless, epidemiologists routinely use measurement methods (including multiplier methods) that assume population stability to estimate changes in prevalence; these methodologies are well-established in the field despite their reliance on an assumption that is known to be imperfect.[8] Defendants offer no cogent reason to question this practice in general and show no actual flaw in Dr. Keyes' analysis.

Third, Defendants argue that Dr. Keyes may not support her computation by referring to its consistency with real-world OUD data because the Rule 702 inquiry looks solely at an expert's methodology, not her conclusions. Reply Br. 11. But comparing her calculated estimate to the number of OUD cases identified in the community by Dr. Todd Davies was, in fact, *part of Dr. Keyes' methodology*, as explained in both her Report[9] and in the September 23, 2020 Second Errata, Dkt. 1097-22, based on Dr. Davies' clarification of the data.[10] This methodology was especially reliable because it included this cross-check with real-world data. Indeed, the text relied upon by Defendants to explain the multiplier method states that "[g]reat caution needs to

[6] Matthew Hickman & Colin Taylor, *Indirect Methods to Estimate Prevalence, in Epidemiology of Drug Abuse* 113, 118 (Zili Sloboda ed., 2005), Dkt. 1160-7.

[7] Hickman, *supra*, at 125 (emphasis omitted).

[8] See, e.g., Kaatje Bollaerts *et al.*, *Improved benchmark-multiplier method to estimate prevalence of ever-injecting drug use in Belgium, 2000–10*, 71 Archives Pub. Health 10 (2013), Ex. B.

[9] Keyes Rep. 43, Dkt. 1097-18.

[10] Keyes Second Errata 2, Dkt. 1097-22.

be exercised when using multiplier studies that are not *confirmed, validated or cross-checked with other studies and other information."*[11] Thus, Dr. Keyes' reference to the real-world count of OUD cases in Cabell/Huntington is part of the multiplier method and precisely the type of validation contemplated by the textbook authors.

Fourth, Defendants argue that a recently published indirect estimate of approximately 1,900 "people who inject drugs" (PWID) in Cabell County undermines Dr. Keyes' estimate of approximately 8,000 residents of Cabell/Huntington with OUD. Defendants' argument overlooks the known fact that OUD is a consequence of *all* types of opioid exposure, e.g., swallowing oxycodone/hydrocodone pills, chewing fentanyl patches, and/or snorting crushed pills or powders of all types of opioids. A study that is explicitly limited to PWID necessarily underestimates the number of OUD cases among Cabell/Huntington residents who use opioids in all routes of exposure.[12]

III. Defendants Offer No Basis for a Discovery Sanction

Defendants contend that their three-hour supplemental deposition of Dr. Keyes was not sufficient opportunity to cure the surprise caused by service of the Second Errata. Reply Br. 16–17. They rely on *Southern States Rack and Fixture, Inc. v. Sherwin-Williams Co.*, 318 F.3d 592, 593–94 (4th Cir. 2003), which involved an expert opinion first disclosed on the third day of trial to argue that the opportunity to cross-examine *at trial* does not cure a lack of disclosure. Here, however, Defendants had the opportunity to cross-examine Dr. Keyes *at a deposition* more than three months before trial. *Southern States* is thus wholly inapplicable. *See Bresler v. Wilmington*

[11] Hickman, *supra*, at 122 (emphasis added).

[12] As an example, one study found that even among heroin users, only about half inject; the other half use other routes. Scott P. Novak & Alex H. Kral, *Comparing Injection and Non-Injection Routes of Administration for Heroin, Methamphetamine, and Cocaine Uses in the United States*, 30 J. Addictive Diseases 248 (2011), Ex. C.

Tr. Co., 855 F.3d 178, 191–92, 194 (4th Cir. 2017) (affirming admission of expert opinion first disclosed nearly two months before trial); *see also Estate of Burns ex rel. Vance v. Cohen*, No. 5:18-cv-00888, 2019 WL 2553629, at *3 (S.D.W. Va. June 19, 2019) (no prejudice where opinion disclosed two weeks late, "several months before trial"); *Kinlaw v. Nwaokocha*, No. 3:17-cv-772, 2019 WL 2288445, at *7 (E.D. Va. May 29, 2019) ("Defendants are permitted to re-depose Dr. Katz, which will allow adequate time for the alleged surprise to the Defendants to be cured" two months before trial).

Defendants also argue that Dr. Keyes's methodology with respect to the treatment of so-called "suppressed data" was not properly disclosed because Dr. Keyes used a different methodology in her Second Errata than the one previously disclosed. This is not so: Dr. Keyes applied the identical methodology as to suppressed data in her Report and her Second Errata. In both cases, Dr. Keyes set the suppressed values to the mid-point—that is, five deaths for every year included in her computation.[13] This was explicitly disclosed in the August 13, 2020 worksheet provided pursuant to Defendants' request, see Br. Opp. 17, and again on September 24, 2020 after Dr. Keyes' first deposition.[14] The difference Defendants claim to discern is simply that the August 13, 2020 worksheet made computations only for the period 2006–2018, while September 24, 2020 worksheet included a computation for the period 1999–2018. In the earlier worksheet, the years 1999, 2000, 2001, 2003 and 2005 were marked "N/A" because they were "not applicable" to the computation of mortality during the period 2006–2018. In the later worksheet, the mid-point was used for all years in which data was suppressed. Thus, whenever

[13] Keyes Rep. 50, Dkt. 1097-18.

[14] See Supplemental Keyes Dep., Oct. 30, 2020, Ex. 10, col. S, Dkt. 1172-1, at 65 (Aug. 13, 2020 worksheet underlying Report and First Errata, Dkt. 1097-21), disclosed by Email, Aug. 13, 2020, Dkt. 1097-20; Supplemental Keyes Dep., Oct. 30, 2020, Ex. 6, col. A, Dkt. 1172-1, at 63 (Sept. 24, 2020 sensitivity analysis underlying Second Errata), disclosed by Email, Sept. 24, 2020, Dkt. 1097-24.

Dr. Keyes included a year that involved suppressed data, she used the mid-point. That some computations did not involve every year only means those years were inapplicable, not that Dr. Keyes used a different methodology to take account of them.[15]

Dated: December 1, 2020

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[15] Defendants cherry-pick years for which the number of fentanyl deaths in Cabell County was zero, which actually undermines their position. If the number of fentanyl deaths had been zero in 1999, 2000, 2001, 2003 and 2005, those would have been reported as zero, rather than reported as having suppressed data. Yet Defendants would argue that Dr. Keyes should have considered those years as having zero deaths—a patently incorrect interpretation of the use of data suppression. If there had been zero deaths, there would have been zero parties whose privacy interests could have been jeopardized by not suppressing.

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Exhibit A

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA

* *

THE CITY OF HUNTINGTON,

Plaintiff,

vs. CIVIL ACTION
NO. 3:17-01362

AMERISOURCEBERGEN DRUG CORPORATION, et al.,

Defendants.

_____

CABELL COUNTY COMMISSION,

Plaintiff,

vs. CIVIL ACTION
NO. 3:17-01665

AMERISOURCEBERGEN DRUG CORPORATION, et al.,

Defendants.

* *

Videotaped and videoconference personal and 30(b)(6) deposition of DR. ALLEN MOCK AS REPRESENTATIVE OF THE WEST VIRGINIA STATE MEDICAL OFFICE taken by the Defendants under the Federal Rules of Civil Procedure in the above-entitled action, pursuant to notice, before Teresa S. Evans, a Registered Merit Reporter, all parties located remotely, on the 14th day of August, 2020.

testimony that OCME has regarding carfentanil?

A. Yes, with the provision that some of my dates may have been incorrect. I think I qualified them as my best estimate, but they -- I'm sure they could be more accurate.

Q. Okay. Does OCME still see carfentanil overdose deaths?

A. Yes.

Q. Are they -- is there an uptick in them, or how -- how is that working?

A. Well, Doctor Gilson has seen a pretty dramatic uptick, and I think Kentucky Greg -- or the chief in Kentucky had seen a similar uptick. I was asked to look into our data informally, and we had an uptick in the last part of 2019. Just by a cursory examination, nothing looked significant on our end. But there was certainly a demonstrable uptick very different than what they saw in Ohio, for example, that was really dramatic.

So I was on high alert to -- you know, obviously carfentanil became of increased scrutiny for me. My threshold for finding it was better attuned.

Q. How many people died in 2019 from

carfentanil?

A. I don't have that data available.

Q. Was there a specific geographic area that you saw an uptick in carfentanil in 2019?

A. I don't recall specifically, but I imagine that there were some that the -- in the bordering areas between Ohio and West Virginia.

Q. Would that include Cabell County?

A. Again, geographically challenged, I don't think Cabell County would be -- it's not terribly close, I don't believe. Yeah, I mean, it potentially could have been. I can't say that there were no cases from Cabell. But it doesn't stand out as a -- you know, a frequent carfentanil death location.

Q. Okay. If you go down to your e-mail to Doctor Hall at 11:35 a.m., you begin with, "I've seen an uptick in cocaine subjectively."

When did you see an uptick in cocaine?

A. I would imagine it's in the 2016 period. It's a -- it's demonstrable now that there's a lot more cocaine than there was back at this time, but I think I just noticed a slight increase in cocaine.

to the opioid crisis and listed various opioids -- heroin and fentanyl and carfentanil -- and as we saw through many of the slides, the prescription opioids too would have contributed to the opioid epidemic?

MS. ZERRUSEN: Objection.

A. Yeah. In a combined intoxication of multiple opioids, then they're all significant. So in a combined intoxication between prescribed Oxycodone and illicitly-manufactured fentanyl, both would be significant, and so both would contribute to those numbers.

MS. KEARSE: Doctor Mock, I have no further questions.

THE DEPONENT: Thank you.

MS. KEARSE: Thank you, and have a great Friday.

THE DEPONENT: You take care.

MS. ZERRUSEN: I have no follow-up.

VIDEO OPERATOR: Are there any further questions?

If there are no further questions, this concludes today's testimony given by Doctor Allen Mock. We are now off the record. The time

Exhibit B

Bollaerts et al. Archives of Public Health 2013, 71:10
http://www.archpublichealth.com/content/71/1/10

ARCHIVES OF PUBLIC HEALTH

RESEARCH Open Access

Improved benchmark-multiplier method to estimate the prevalence of ever-injecting drug use in Belgium, 2000–10

Kaatje Bollaerts[1*], Marc Aerts[2] and Andre Sasse[1]

Abstract

Background: Accurate estimates of the size of the drug-using populations are essential for evidence-based policy making. However, drug users form a 'hidden' population, necessitating the use of indirect methods to estimate population sizes.

Methods: The benchmark-multiplier method was applied to estimate the population size of ever injecting drug users (ever-IDUs), aged 18–64 years, in Belgium using data from the national HIV/AIDS register and from a sero-behavioral study among injecting drug users. However, missing risk factor information and absence of follow-up of the $HIV^+/AIDS^-$ cases, limits the usefulness of the Belgian HIV/AIDS register as benchmark. To overcome these limitations, statistical corrections were required. In particular, Imputation by Chained Equations was used to correct for the missing risk factor information whereas stochastic mortality modelling was applied to account for the mortality among the $HIV^+/AIDS^-$ cases. Monte Carlo simulation was used to obtain confidence intervals, properly reflecting the uncertainty due to random error as well as the uncertainty associated with the two statistical corrections mentioned above.

Results: In 2010, the prevalence (/1000) of ever-IDUs was estimated to be 3.5 with 95% confidence interval [2.5;4.8]. No significant time trends were observed for the period 2000–2010.

Conclusions: To be able to estimate the ever-IDU population size using the Belgian HIV/AIDS register as benchmark, statistical corrections were required without which seriously biased estimates would result. By developing the improved methodology, Belgium is again able to provide ever-IDU population estimates, which are essential to assess the coverage of treatment and to forecast health care needs and costs.

Keywords: Population size estimation, Ever injecting drug use, Benchmark-multiplier method, HIV/AIDS register, Imputation by Chained Equations, Stochastic mortality modelling

Background

Accurate estimates of the size of the drug-using population are indispensable to govern and evaluate drug policy. They are particularly important to forecast health care needs and costs and to assess the coverage of treatment and harm reduction measures e.g. [1,2]. However, drug users form a `hidden' population, hiding their membership because it involves illegal and stigmatized behaviour. As a result, `hidden' populations lack sampling frames and classical epidemiological methods (e.g. population-based surveys) fail. Therefore, indirect estimation methods are to be used. Generally, three types of indirect estimation methods are distinguished to estimate the size of drug using populations: capture-recapture (CR), benchmark-multiplier (BM) and multivariate indicator (MI) methods [3-5]. An application of the BM method is presented in this paper.

The BM method is a very intuitive method, relatively easy to apply and hence, frequently used [6]. The BM method combines (an estimate of) the size of the known part of the target population, the benchmark, with an estimate of the proportion of individuals from the target

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population belonging to the benchmark. The reciprocal of the proportion is called the multiplier. The size of the target population is then estimated as the product of the benchmark and the multiplier. Common sources used as benchmark are mortality registers, HIV/AIDS registers, drug treatment or police data e.g. [7,8]. During the beginning of the 1970s, the mortality multiplier method was already used [9]. Multiplier methods e.g. [10,11] have produced estimates consistent with estimates produced by CR methods, which have been put forward as a preferred methodology [6]. The key assumptions underlying the BM method are that the benchmark should be exhaustive, the sample used to estimate the multiplier should be representative of the target population and the case definition used for the benchmark should exactly match the one used for the multiplier, including the time window [12].

In this paper, the benchmark-multiplier (BM) method was applied to estimate the prevalence of ever injecting drug users (ever-IDUs) within the population aged 15–64 years in Belgium, 2000–10, using the HIV/AIDS register as benchmark. In Belgium, HIV-screening is widely used and all sera of which the screening test result was positive, are submitted for confirmation to one of the seven AIDS Reference Laboratories (ARLs) in Belgium. The registration results of all ARLs are then send to the national HIV/AIDS register. As the seven ARLs are the only laboratories subsidized for performing HIV confirmation tests, the Belgian HIV/AIDS register is deemed to be exhaustive and hence, constitutes a potential suitable benchmark.

For Belgium, the latest estimate of the ever-IDU prevalence date from 1995 and was obtained adopting the BM approach using the HIV/AIDS register as benchmark [13]. However, the Belgium HIV/AIDS register suffers from missing risk factor information. Particularly, of all registered cases in 2000–10, 28.6% were reported without information on probably mode of HIV transmission (e.g. sexual contact, blood transfusion, injecting drug use). Simply discarding these cases from analysis would lead to an underestimation of the IDU prevalence. Simply extrapolating the risk factor fractions of the subpopulation for which the risk factors are known to the subpopulation for which they are unknown, would lead to overconfident results and would only lead to unbiased results under very strict assumptions (i.e. the Missing Completely ad Random assumption). In addition, the national HIV/AIDS register lacks follow-up of the non-AIDS cases, implying absence of information on the vital status of the $HIV^+/AIDS^-$ cases. Not accounting for the mortality among these cases would result in an overestimation of the number of alive seropositive IDUs, with the bias increasing as the time since the onset of the HIV-epidemic (mid-eighties) increases. The methodology proposed in [13] used a simple extrapolation method to account for the missing risk factor information and failed to account for the mortality among $HIV^+/AIDS^-$ cases. Therefore, the current paper presents an improved application of HIV/AIDS BM method, using up-to-date statistical methods to correct for the missing risk factor information and lacking follow-up of the $HIV^+/AIDS^-$ cases.

Methods

Benchmark: national HIV/AIDS register

During 2000–10, an average of 56 screening tests per 1000 inhabitants per year were performed in Belgium, excluding tests related to blood donations (National Institute for Sickness and Invalidity Insurance). The confirmation tests are performed by one of the seven ARLs in Belgium, being the only laboratories subsidized for performing these tests. The registration results of the seven ARLs are validated for duplicate recording and are all included in the national HIV/AIDS register, being hosted by the Scientific Institute of Public Health, Brussels (WIV-ISP). Since its foundation in 1985–86, the Belgian HIV/AIDS register is deemed to be exhaustive.

For each confirmed HIV-positive test, a standardized form is sent to the patient's clinician to collect additional information on nationality, residence, sexual orientation, probable mode of HIV transmission and CD4 count at time of HIV diagnosis. The response categories for the self-reported probable mode of HIV transmission are homo- and heterosexual transmission, transmission through blood transfusion, transmission through injecting drug use and mother-to-child transmission. A person can indicate multiple modes of transmission. Unfortunately, the standardized forms are not always fully completed returned to the WIV-ISP, resulting in missing risk factor information.

Follow-up is conducted for patients who developed AIDS with each year data being collected on last consultation and possible death. The variables available for the AIDS cases are year at AIDS-diagnosis, year at death and year at lost to follow-up, which are only completed upon occurrence of the event and hence, are time dependent. The $HIV^+/AIDS^-$ cases are not subject to follow-up.

Multiplier: sero-behavioral prevalence study

In Belgium, a sero-behavioral study among drug users in contact with drug treatment facilities or imprisoned was carried out in 2004–05 [14]. In total, 1005 drug users in treatment and 117 incarcerated drug users (15–40 years) enrolled at 65 different drug treatment facilities and 15 different prisons geographically dispersed over Belgium, respectively, participated to the study. Of the drug users in treatment and in prison, 57% (n = 573) and 68% (n = 80) declared to have injected drugs at least once during their life. Intravenous blood samples were taken to determine the HIV- as well as the Hepatitis B and -C status of the

participants. The HIV-seroprevalence among IDUs in treatment and in prison was estimated to be 2.8% (95% Wald CI: [1.5;4.2]) and 5% (95% Wald CI:[0.2;9.9]), respectively. These prevalences were not significantly different (p-value = 0.30), yielding an overall estimated prevalence of 3.1% (95% Wald CI: [1.8;4.8]).

In addition to serological studies, the HIV prevalence among IDUs in Belgium can be obtained from routine diagnostic testing, of which the results are yearly available. This allows the investigation of time trends. However, a concern regarding the (geographical) representativeness of the Belgian data exists. In line with (Western) European trends [15], no significant time trends in HIV prevalences among IDUs were observed during the last 10 years in Belgium based on the results from routine diagnostic testing [16]. Therefore, the HIV prevalence from the sero-behavioral study was assumed to apply for the entire period 2000–10.

Statistical methods

An estimate of the prevalence of ever-IDUs was obtained by means of the BM method. For the current application, the benchmark N_x was the number of alive seropositive ever-IDUs (aged 18–64 years) in Belgium for a given year. The benchmark N_x was obtained from the national HIV/AIDS register after correcting for the missing risk factor information using Imputation by Chained Equations [17-19] and after correcting for the lacking information on the vital status of the $HIV^+/AIDS^-$ cases using stochastic mortality modelling [20]. The multiplier π was then the reciprocal of the HIV-prevalence among the ever-IDUs, for which an estimate could be obtained from the sero-behavioral study by Plasschaert et al. [14]. A 3-step Monte Carlo simulation model was built to generate (interval) estimates of the prevalence of ever-IDUs. A schematic overview of the 3-step simulation model is provided in Table 1. The different steps within the simulation model are described in more detail below. This model was run K = 1000 times, yielding K = 1000 different estimates of the ever-IDU prevalence, based on which the 95% percentile Monte Carlo confidence intervals (95% MC CIs) were calculated.

Step 1: To correct for the missing risk factor information, *Imputation by Chained Equations* (ICE) was used. ICE is an iterative technique that starts by filling in the missing values in a simple way, e.g. by using mean imputation [17-19]. Then, each variable included in the imputation model X_i, $i = 1, 2,\ldots q$, is imputed in turn by the predictions of the regression model regressing the observed values of X_i on the observed and imputed values of the remaining variables within the imputation model. The iteration through all q variables constitutes one cycle. After a sufficient number of cycles (typically 10 cycles), the final imputations are retained, resulting in one 'complete' dataset. There are several software packages available providing (M)ICE procedures, i.e. STATA [21], S-PLUS or R [22]. For the current application, ICE as implemented in STATA was used to account for the missing risk factor information. In particular, the imputation model included all (auxiliary) variables that had a statistically significant association with the variable indicating whether injecting drug use was the most probable route of transmission; being sex, nationality, year at registration and age at registration. For every run k ($k = 1,2,\ldots K = 1000$), one 'complete' dataset was generated.

Table 1 Schematic overview of the 3-step Monte Carlo simulation model to estimate ever IDU prevalences‡

STEP 1:	**Imputation by Chained Equations: missing risk factor information**
	Missing risk factor information was imputed using Imputation by Chained Equations. The imputation model contains the variables: injecting drug use, sex, nationality, year at registration and age at registration. The imputation results in one complete dataset $\mathbf{X_k}$, containing original and imputed values.
STEP 2:	**Stochastic Mortality Modeling: lacking follow-up of the $HIV^+/AIDS^-$ cases**
	For a complete dataset k, the number of registered HIV-cases for whom injecting drug use was the most probable route of transmission and who were alive at time t is calculated as $\hat{N}_x^k(t) = \sum_{i=1}^{n_t} \left(I_i^k \middle| X_{3\,i}^k = 1\right)(t)$ *with* $I_i^k = \begin{cases} 0, & T_{d\,i} < t \text{ or } T_{l\,i} < t \\ 1, & T_{a\,i} \geq t \text{ or } T_{d\,i} \geq t \text{ or } T_{l\,i} \geq t \\ S_i \sim bern\left((1-p_d)^{r_i}\right), & otherwise, \end{cases}$ where I_i indicates the 'vital' status with $I_i = 1$ if person i is still alive and living in Belgium and $I_i = 0$ otherwise, where r_i is the number of years since HIV registration or $r_i = t - t_{hi}$ and where p_d is the annual non-AIDS mortality rate among seropositive IDUs with $p_d \sim betapert$*(0.58%, 1.08%, 1.58%).
STEP 3:	**Benchmark-multiplier method: population size estimation**
	The number of ever-injecting drug users being alive at time t is given by $\hat{N}_y^k(t) = \hat{p}_{HIV}^{-1}\hat{N}_x^k(t) - n^{-1}\hat{N}_x^k(t)(1-\hat{p}_{HIV})\hat{p}_{HIV}^{-1}$, with $\hat{N}_x^k(t)$ obtained from step 2, $\hat{p}_{HIV} \sim beta(21,620)$ and $n = 639$.

‡ The model was run K = 1000 times.
* The betapert distribution is mainly used to model expert estimates and requires a minimum, most likely and maximum value.

Step 2: *Binomial stochastic mortality modelling* was applied to correct for the lacking information on the vital status of the $HIV^+/AIDS^-$ cases. More precisely, the vital status of a $HIV^+/AIDS^-$ case i was simulated using a binomial process having survival probability $p_i = (1 - p_d)^{r_i}$ with r_i being the number of years since HIV registration, implying lower survival probabilities when the time since HIV-registration increases. The non-AIDS crude mortality rate among IDUs (p_d) was assumed to follow a betapert distribution [23] with minimum, most likely and maximum values of 0.58%, 1.08% and 1.58% per annum, respectively. These non-AIDS crude mortality rates were calculated by Degenhardt et al. [24] based on 44 cohort-studies. The vital status of the AIDS cases at time t was deduced from the AIDS-specific variables year at AIDS-diagnosis (T_a), year at death (T_d), and year at lost to follow-up (T_l). In particular, an AIDS case was indicated to be alive at time t if any information was recorded after time t (i.e. if $T_a \geq t$ or $T_d \geq t$ or $T_l \geq t$). On the other hand, an AIDS case was indicated to be death at time t if the person died before time t or was lost to follow-up. In the latter case, the person is most likely to be death or to have left the country.

Step 3: The *Benchmark Multiplier method* was obtained to estimate the size N_y of the partly 'hidden' population or the target population as

$$\hat{N}_y = \frac{\hat{N}_x}{\hat{\pi}}, \quad (1)$$

having estimated benchmark $\hat{N}_x$ and estimated multiplier $\hat{\pi}^{-1}$. However, even if $\hat{N}_x$ and $\hat{\pi}$ are unbiased estimators, $\hat{N}_y$ is a biased estimator of N_y because of its non-linearity with respect to $\hat{\pi}$. Therefore, the bias-corrected estimator as proposed in (Bollaerts K, Sasse A, Aerts M: The benchmark-multiplier method: bias and new bias-corrected estimator. *In preparation*) was used or

$$\hat{N}_y^{BC} = \frac{\hat{N}_x}{\hat{\pi}} - \frac{1}{n}\hat{N}_x\frac{(1-\hat{\pi})}{\hat{\pi}}, \quad (2)$$

with n being the size of sample used to estimate π. Observe that the sample size n is the only additional piece of information needed to construct the bias-corrected estimator as compared to the traditional estimator. Then, the estimate of the benchmark $\hat{N}_x$ was obtained from step 1 and 2 whereas the estimate $\hat{\pi}$ and the corresponding sample size n were derived from the sero-behavioral prevalence study [14]. As the study indicated that x = 20 out of the n = 639 ever-IDUs were seropositive, $\hat{\pi}$ was assumed to follow a beta distribution with $\hat{\pi} \sim beta(x+1, n-x+1)$ or $\hat{\pi} \sim beta(21, 620)$ [25].

Results

After having corrected for missing risk factor information, a total of 845 HIV-cases (aged 18-64yrs) with the HIV-infection probably related to injecting drug use has been identified in Belgium up to the year 2000. This number increased to 1113 in 2010. Correcting for $HIV^+/AIDS^-$ mortality, these numbers dropped to 642 and 809 alive HIV^+ ever-IDUs in 2000 and 2010, respectively. In 2010, the total number of ever-IDUs (aged 18-64yrs) was estimated to be 24664 (95% MC CI: [17565;34403]) with the corresponding prevalence (/1000) being 3.5 (95% MC CI: [2.5;4.8]). No significant time trends in the number of ever-IDUs were observed (Table 2).

Table 2 Results of the Monte Carlo (MC) simulation study estimating the prevalence of ever Injecting Drug Use (IDU), Belgium, 2000-10

	Number of seropositive IDUs		Number of alive seropositive IDUs		Number of alive IDUs		Prevalence (/1000)	
Year	Est*.	95% MI CI ǂ	Est*.	95% MI CI ǂ	Est*.	95% MI CI ǂ	Est*.	95% MI CI ǂ
2000	845	[814;877]	642	[612;673]	19497	[13540;27010]	2,9	[2.0;4.0]
2001	876	[848;906]	659	[630;690]	19989	[14147;27663]	3	[2.1;4.1]
2002	909	[879;940]	682	[654;713]	20721	[14724;28166]	3,1	[2.2;4.2]
2003	961	[932;993]	723	[692;755]	22191	[15927;30659]	3,3	[2.3;4.5]
2004	995	[964;1028]	744	[712;775]	22861	[16220;31947]	3,4	[2.4;4.7]
2005	1009	[978;1042]	749	[719;781]	22653	[15743;31955]	3,3	[2.3;4.7]
2006	1031	[997;1063]	758	[726;790]	23178	[16362;31976]	3,4	[2.4;4.6]
2007	1061	[1029;1095]	779	[747;812]	23704	[16583;32937]	3,4	[2.4;4.7]
2008	1080	[1049;1112]	792	[761;826]	24026	[16844;32958]	3,4	[2.4;4.7]
2009	1094	[1062;1127]	798	[766;831]	24358	[17013;33951]	3,4	[2.4;4.8]
2010	1113	[1079;1147]	809	[775;842]	24664	[17565;34403]	3,5	[2.5;4.8]

* Est.: mean estimate; ǂ 95% MC CI: 95% Monte Carlo Confidence Intervals.

Discussion

To obtain recent estimates of the ever-IDU prevalence in Belgium, an improved HIV multiplier method was applied. The improved methodology allows using the Belgian HIV/AIDS register as benchmark while accounting for missing risk factor information (through Imputation by Chained Equations - ICE) and lacking follow-up of the $HIV^+/AIDS^-$ cases (through stochastic mortality modelling). The statistical corrections were implemented in the best possible way. Indeed, ICE is a very flexible imputation approach, that can deal with several incomplete variables, does not require specific missing data patterns and operates under the less stringent assumption that the probability of the missing values depends only on the observed values and not on unobserved values (the so-called Missing at Random assumption, [26]) [17-19]. The stochastic mortality model accounts for the uncertainty in the mortality rate and the Monte Carlo simulation model properly acknowledges the uncertainty associated with the statistical corrections mentioned above.

In 2010, the prevalence (per 1000 inhabitants, 15–64 years) of ever injecting drug use in Belgium was estimated to be 3.5 (95% CI: 2.5-4.8), with no significant time trends being observed for the period 2000–10. Similar findings were reported by the other European countries providing time trends of the national prevalence of ever injecting drug use, i.e. Norway, Cyprus and the Czech republic [15]. This absence of a time trend is seemingly in contrast with recent findings from the EMCDDA treatment demand indicator, suggesting a decline in recent-onset heroin users and heroin injectors in the Western European countries [27]. However, it need to be stressed that the prevalence of ever injecting drug use is less sensitive to recent trends in drug use.

The above mentioned results should also be regarded in the light of the assumptions underlying the BM method. Particularly, the BM estimates rely on the conditions that the benchmark is complete and that the multiplier is estimated based on a representative sample of the target population. As benchmark of the current analysis, the national HIV/AIDS register was used. Since its foundation, the Belgian HIV/AIDS register is deemed to be exhaustive as it includes the results of all Belgian laboratories subsidised for performing HIV confirmation tests. As not only AIDS cases but also HIV cases are registered, the Belgian HIV/AIDS register has the additional advantage that back-calculation methods are not needed to obtain the HIV prevalence. The multiplier was obtained from a national sero-prevalence study including 653 IDUs [14]. Although this is the largest and most recent Belgian sero-prevalence study, it did not include IDUs outside treatment/prison, for whom currently no information is available. Despite the fact that low threshold drugs services are common in Belgium, the possibility of bias resulting from a multiplier derived from a sample that is not fully representative of the target population cannot be ruled out.

To summarize, the current paper provides a thorough application of the BM method. Nevertheless, the use of such indirect methods inherently relies on empirically non-verifiable (but reasonable) assumptions, such as the representativeness of the multiplier. Therefore, the current estimate of the ever IDU prevalence should be complemented with estimates based on other data sources (e.g. substitution treatment register) and/or using other methods (e.g.capture-recapture, multivariate indicator method) (e.g. [28]). For now, it is (reasonably) assumed that the HIV prevalence among IDUs remained stable during the last ten years. However, new prevalence estimates are needed for future applications of the BM method based on the Belgian HIV/AIDS register. Finally, this paper presents estimates of the ever IDU prevalence, which are important to assess future health care needs regarding e.g. Hepatitis C treatment. However, when interest is in assessing the coverage adequacy of needle exchange programmes (NEPs) or opioid substitution treatment (OST), national estimates of the current IDU prevalence are required. The latter prevalence (per 1000 inhabitants, 15–64 years) can be roughly estimated as 1.4 (95% CI: 1.02-1.97) by multiplying the ever-IDU prevalence with the ratio between current injectors and ever injectors (r = 41%) among all treatment demands as provided by the treatment demand indicator [29].

Conclusion

As the latest estimates of the prevalence of ever-IDUs for Belgium date from 1995 [13], obtaining new estimates was prioritized. To be able to estimate the ever-IDU population size adopting the BM approach using the Belgian HIV/AIDS register as benchmark, statistical corrections were required. In particular, not accounting for the mortality among $HIV^+/AIDS^-$ cases would nowadays results in seriously biased estimates. By developing the improved methodology, recent ever-IDU population estimates for Belgium could be obtained. These estimates are essential to monitor trends over time and to forecast health care needs and costs (e.g. for Hepatitis C treatment).

Competing interests

The authors declared that they have no competing interests.

Authors' contributions

KB conceived and carried out the statistical analysis and drafted the paper. AS provided substantial intellectual input regarding the use of the HIV/AIDS register and critically revised the manuscript. MA provided substantial intellectual input regarding the statistical analysis and critically revised the manuscript. All authors read and approved the final manuscript.

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Exhibit C

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Comparing Injection and Non-Injection Routes of Administration for Heroin, Methamphetamine, and Cocaine Uses in the United States

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Abstract

Research examining the demographic and substance use characteristics of illicit drug use in the United States has typically failed to consider differences in routes of administration, or has exclusively focused on a single route of administration--Injection Drug Use (IDU). Therefore, a significant gap exists in our understanding of the degree to which IDUs are different from those who use illicit drugs via other routes, such as oral, inhalation, or smoked (non-IDUs). Data from the 2005–2007 National Survey on Drug Use and Health (NSDUH) were used to compare past-year IDU and non-IDU routes of administration for people who use the three drugs most commonly injected drugs in the US: heroin, methamphetamine, and cocaine. Among past-year users, IDUs were more likely than those using via other routes to be older (aged 35+), unemployed, possess less than a high school education, and reside in rural areas. IDUs also exhibited higher rates of abuse/dependence, perceived need for substance abuse treatment, and co-occurring physical and psychological problems. Fewer differences between IDUs and non-IDUs were observed for heroin users compared to methamphetamine or cocaine users. These results highlight significant differences in demographics, clinical/psychological manifestations, and treatment needs of injection drug users compared to those engaging in other routes of administration.

Keywords

Injection drug use; cocaine; methamphetamine; heroin; routes of administration; epidemiology

Introduction

Much of the past research on illicit drug use conducted over the last several decades has focused on how users differ in their risk factor profiles, sequence of involvement across various drugs, consumption trajectories (i.e., quantity/frequency), likelihood to progress to abuse/dependence, and treatment response (Kandel, Yamaguchi, & Klein, 2006; McLellan, McKay, Forman, Cacciola, & Kemp, 2005; Vega et al., 2002). Less is known about the effects of different routes of self-administration, including injection (subcutaneous, intramuscular, intravenous), oral ingestion, smoking, and nasal inhalation methods. This

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lack of attention is notable, because the way in which a drug is ingested significantly affects how it is metabolized by the body (i.e., pharmacokinetics), and hence, the immediate and long-term psychological and physiological responses to its use (McKim, 2000). An emerging trend in substance abuse interventions is to develop pharmacological and behavioral treatments that are tailored to the unique needs of individual users (Ducharme, Knudsen, & Roman, 2006; Geppert & Bogenschutz, 2009; Grella, 2008; Schnabel, 2009). By learning more about how routes of administration are related to user characteristics, we could improve our ability to tailor substance abuse treatment and prevention strategies to individual users.

Injection drug use appears to be the most harmful route of administration. This is most likely because of the transmission of blood borne diseases such as HIV and hepatitis C virus through needle sharing (Des Jarlais et al., 2003; Kral, Bluthenthal, Erringer, Lorvick, & Edlin, 1999; Thomas et al., 1996). IDUs also suffer a disproportionate risk of overdose (Sterrett, Brownfield, Korn, Hollinger, & Henderson, 2003; Warner-Smith, Darke, & Day, 2002) and represent the highest proportion of those involved in the substance abuse treatment system (Amodeo, Lundgren, Chassler, & Witas, 2008; Chassler, Lundgren, & Lonsdale, 2006; SAMHSA, 2007). The preclinical literature also justifies focusing on IDUs as a unique population. Laboratory studies have shown that IDU carries the highest abuse potential because it delivers a large bolus of the drug directly into the blood stream, which is then rapidly transported to the brain. In contrast, drugs ingested via other routes (e.g., smoking/inhalation) are filtered through the lungs and/kidneys before being absorbed into the brain (Vann et al., 2009, Porrino 1993). While it is readily acknowledged that injection drug use is physiologically different when compared to other routes of administration, the vast community-based substance abuse research literature has failed to identify and directly test the degree to which IDUs represent a distinct population based on demographic characteristics, usage patterns, and psychosocial profile. The few studies comparing IDUs and non-IDUs have primarily examined differences in routes of administration for only a single drug, such as heroin, or used samples drawn from rather homogenous populations, such as regional studies of street-based users in a single metropolitan area (Barrio et al., 2001; Gossop, Marsden, Stewart, & Treacy, 2000). A study with a large, geographically diverse sample of IDUs and non-IDUs involved with different usage patterns of several types of illicit drugs would help determine whether IDUs are really a distinctive class of users with unique etiologies as well as prevention and intervention needs. The current study addresses this important gap in the literature using a large, nationally diverse sample of IDUs and non-IDU to identify potential differences in the demographic, psychological, and substance use profiles.

Methods

Sample

This study combines repeated cross-sectional data (2005–2007) from the National Survey on Drug Use and Health (NSDUH), which is an annual, nationally representative survey of youth (age 12–17) and adults (age 18 or older) in the United States. The procedures and characteristics of the sample have been published extensively elsewhere (SAMHSA, 2008). Briefly, the sample includes approximately 65,000 respondents each year. The target population is the civilian, noninstitutionalized population of the United States (including civilians living on military bases) and residents of noninstitutional group quarters (e.g., college dormitories, group homes, civilians dwelling on military installations) and persons with no permanent residence (homeless people in shelters and residents of single rooms in hotels). As much of the prior research on IDU has used local, community-based samples, the NSDUH provides an important complement to these prior field studies.

Instrument and Measures

The NSDUH collects information on a large range of illicit substances, including consumption patterns, treatment utilization, and diagnoses aligned with the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for abuse and/or dependence (APA, 2000) for alcohol and selected drugs. Beginning in 2005, the NSDUH expanded the non-core instrument to include additional items on routes of administration for illicit drugs used in the past-year, including injection, oral, nasal inhalation, and smoking. These items were asked in reference to the following three substances: heroin, methamphetamine, and cocaine. Lifetime usage questions were also asked in an open-ended format in which a respondent could list any drug they had ever injected. The rationale for focusing on heroin, methamphetamine, and cocaine is that preliminary analyses indicated that over 90% of lifetime injectors reported injecting at least one of these three drugs. The remaining 10% were distributed among a wide array of drugs with extremely small sample sizes, including prescription drugs (opiates, stimulants), steroids, PCP, and LSD. We categorized routes of administration into a dichotomous variable of IDU and non-IDU for each drug. Epidemiological evidence reviewed above suggests that injection has more deleterious health consequences than other forms of ingestion. Therefore, we coded respondents as engaging in IDU even if they had also reported use via another route.

In terms of psychosocial characteristics, a single question assessed perceptions of general health status. The occurrence of a major depressive episode (MDE) in the past-year was also assessed using established clinical DSM-IV criteria (SAMHSA, 2009). Substance use treatment received was coded if the respondent reported receiving therapy or treatment, including detoxification and treatment for any medical problems associated with their drug use. Unmet treatment need was defined as the presence of a past-year DSM-IV diagnosis for abuse and/or dependence on heroin, methamphetamine, or cocaine, but the respondent did not report receiving substance abuse treatment. Key demographic variables included sex, age, race, marital status, employment, US veteran, and urbanicity.

Analyses

All analyses were restricted to past-year users of heroin, methamphetamine, or cocaine, unless otherwise noted. First, we used cross-tabulations to characterize the demographic profile of IDUs compared to other routes of administration. Bivariable and multivariable logistic regression models were also used to identify the most informative discriminators between IDU and non-IDU routes of administration. Second, we examined whether IDUs and non-IDUs differed by co-occurring substance use disorders, psychological and behavioral risks, and treatment utilization. We also further probed whether these relations varied by type of drug (i.e., heroin, methamphetamine, and cocaine) used in the past-year. It is important to clarify that for these latter analyses, a respondent may be classified as an IDU for one substance and a non-IDU for another substance. This variable-centered strategy allowed us to examine how characteristics related to IDU may vary across substances of abuse. This approach differs from a more complex person-centered strategy that would seek to investigate subtypes of users based on the number and types of drugs ingested as well as their route of administration. Finally, we present the magnitude of the observed statistically significant effect sizes estimated using procedures outlined by Cohen (1988). An important caveat about statistical significance tests and measures of effect sizes is warranted. These parameters should always be interpreted with an eye toward discerning whether the observed differences are also meaningful in terms of clinical and public policy. Therefore, effect sizes (e.g., Cohen's *d*) are perhaps most useful as a standardized measure for comparative examination of effects across studies that use similar populations, designs, and measures (e.g., meta-analyses). They are also use for studies that projecting the impact of changes in clinical and/or public health interventions (e.g., simulation/predictive modeling.

Due to the complex sampling design of the NSDUH, all descriptive and inferential analyses were conducted with SUDAAN release 10.0 (RTI, 2009). SUDAAN incorporates the sample weights of the NSDUH to create nationally representative estimates. It also implements a Taylor series linearization to account for the NSDUH's multistage probability sampling design. It also accommodates domain-level analyses, which occur when analyses are conducted on subpopulations (e.g., past-year illicit drug users) selected from the larger study sample. For this project, multiple years of NSDUH data were combined to increase the sample of injection drug users, so additional corrections to the weights and variance estimation were implemented. All statistically significant results described below exhibited p-values below the standard .05 threshold level for a two-tailed test.

Results

Routes of Administration

Of the combined 166,619 respondents aged 12 or older that completed the NSDUH survey between 2005 and 2007, a weighted percentage of 2.69% reported any past-year use of heroin (0.19%), methamphetamine (0.56%), or cocaine (2.36%). Slightly less than 7% (0.17% of 2.69% shown in Table 2) of past-year users reported injecting these drugs. About half of heroin users injected, compared to 13% of methamphetamine users and 3% of cocaine users. Among all past-year IDUs, heroin was the most preferred drug (53%), followed by methamphetamine (43%) and cocaine (40%). A large percentage (66%) of the IDUs reported injecting only one type of drug, which was nearly evenly divided between heroin (39%) and methamphetamine (41%). The remaining 18% injected only cocaine. A relatively small percentage (4%) of past-year IDUs injected all three drugs.

Demographic Characteristics of IDUs and Non-IDUs

Compared to those using heroin, methamphetamine, and cocaine via routes other than IDU, the odds of being an IDU in the past-year were significantly lower among the employed, either full or part-time, college graduates, or those living in major metropolitan areas (see Table 1). These statistically significant findings observed in the bivariable models also remained significant in the multivariable models that controlled for all variables listed in Table 1. Strong racial disparities were observed in the multivariable model, where whites (6.9%) were more likely to be IDUs than either blacks (4.9%) or those classified as "other" racial minority groups (3.5%). No differences were observed between white (6.9%) and Hispanics (6.7%), as the estimated odds for both the bivariable and multivariable models were close to 1.0. An age-graded effect was present such that rates of IDU were higher for each successive age cohort. Gender and veteran status were not significantly associated with injection drug use.

Prevalence of Co-Occurring Health Conditions and Treatment Needs among IDUs and Non-IDUs

IDUs had significantly poorer health outcomes than non-IDUs, including lower perceived general health (21% versus 13% reporting fair/poor health; $p<0.05$) and a higher prevalence of major depressive episodes (26% versus 18%; $p<0.05$) (see Table 2). IDUs also had higher rates of arrests in the past-year (50% versus 19%; $p<0.05$). The prevalence of STDs was similar among IDUs and non-IDUs (11% versus 8%; $p>0.05$).

In terms of substance use characteristics, over half (60%) of IDUs met the DSM-IV criteria for abuse and/or dependence compared to slightly less than one-third (27%) of non-IDUs ($p<0.05$). Almost half (44%) of IDUs exhibited a co-occurring illicit drug use disorder compared to 24% of non-IDUs ($p<0.05$). With the exception of alcohol use disorders, the prevalence of substance use disorders was higher among IDUs, so it is not surprising that the

likelihood of treatment was nearly 4 times as higher (42% versus 11%) for IDUs. However, among those exhibiting a substance use disorder, there was a higher unmet need for treatment for non-IDUs relative to IDUs (75% versus 47%; $p<0.05$). A larger percentage of IDUs reported a need for substance abuse treatment compared to non-IDUs (19% versus 7%; $p<0.05$). As reported in Table 3, all the statistically significant effect sizes met Cohen's threshold for a large effect (0.8 or higher).

Differences by Type of Drug

The final step of our analyses was to examine differences between IDUs and non-IDUs in outcomes by the type of drug used in the past-year. Overall, the findings for the substance-specific models were similar to the full models that combined the substances by route of administration with some notable exceptions. Heroin IDUs tended to resemble non-IDUs, as evidenced by the limited number of statistically significant differences (i.e., two of ten outcomes examined). In contrast, the profile of outcomes tended to be much worse for IDUs compared to non-IDUs for methamphetamine users (i.e., four of ten outcomes) and cocaine users (i.e., eight of ten outcomes). However, a higher proportion of IDUs of heroin met criteria for abuse and/or dependence and exhibited higher odds of being in treatment.

Discussion

The results reported herein show that IDUs represent a relatively unique type of illicit substance user, with distinct demographic characteristics, usage patterns, and psychosocial profiles. Our findings indicate that injection drug use is associated with substantially more substance abuse-related problems, including a higher prevalence of abuse/dependence, unemployment, and co-occurring mental and physical disorders. McLellan and colleagues (2000) note that addiction is a chronic and relapsing disorder that is characterized by a progression of steps from initial to increasing use, then compulsive use with a high frequency of relapse (McLellan, Lewis, O'Brien, & Kleber, 2000). Findings from this study indicate that IDUs are clearly at the high-end of this addiction spectrum, and likely require specialized interventions. According to Lau (2006), interventions should be tailored to specific populations when the target group and the general population show differences in: 1) etiology: risk or protective factors; (2) nosology: symptom patterns or clinical manifestations; 3) treatment response; or 4) treatment engagement: participation, attrition, adherence (Lau, 2006). Our findings support the first two conditions. We identified differences between IDUs and non-IDUs in potential etiological mechanisms (e.g., major depressive episodes) as well as problem phenomenology (e.g., prevalence of abuse/dependence and co-occurring substance use disorders).

Many pharmacological and behavioral studies have shown efficacy in treating opiate (e.g., buprenorphine) or stimulant (e.g., Matrix model) addiction.(Fareed, Vayalapalli, Casarella, Amar, & Drexler, 2010; Shoptaw, Rawson, McCann, & Obert, 1994). While these studies include IDUs as part of the patient population, only rarely are analyses conducted that specifically test the robustness of these interventions to the user's preference for route of administration. Therefore, efforts are needed to understand and potentially expand the repertoire of evidence-based treatments that are available to frontline treatment providers to address unique subpopulations based on different routes of administration (NIDA, 1999; SAMHSA, 2009). For example, we observed that IDUs have higher rates of co-occurring major depressive disorder. This suggests that interventions for IDUs should also consider the types of co-morbidity between mental and addictive disorders. In preparation for the development of specialized interventions for IDUs, the framework from Lau (2006) highlights that comparative effectiveness studies are needed to examine how IDUs may differ in their treatment response to behavioral and pharmacological therapies. As findings from the current work suggest, IDUs face a large number of problems related to substance

use, and these problems appear to characterize a treatment resistant population in need specialized treatments.

The placement of these interventions is also important. Since IDUs are disproportionately engaged in the criminal justice system, criminal justice diversion programs, such as Drug Courts, and treatment for incarcerated offenders should also consider the unique needs of IDUs. In contrast, the subpopulation of non-IDUs may not adequately access HIV/substance abuse information, STD testing and prevention/treatment tools (e.g., syringes/condoms) offered by existing public health interventions such as syringe exchange programs (Bluthenthal, 1998).

Some additional differences between IDUs and non-IDUs observed in this study deserve comment. The finding that heroin IDUs were similar to non-IDU of heroin is notable. Latkin et al. (2001) also concluded that heroin users represent a homogenous class in finding no differences in dependence, though they did observe that IDUs had higher utilization of health care. This is likely due to complications related to risky injection practices, such as infectious diseases and soft-tissue infections (Ciccarone et al., 2001). Barrio et al. (2006) found that while no differences in rates of dependence were observed between IDUs and other routes of administration for heroin, IDUs had a faster progression to dependence. Another consideration is that the different heroin morphologies, such as “black tar” heroin (BTH) and powered heroin (PH) affect injection practices. In the United States, a study by Ciccarone and Bourgois (2004) observed that the chemical properties of BTH may contribute to safer injection practices (Ciccarone & Bourgois, 2003). Using ethnographic data, they describe how BTH often clogs injection needles, thus limiting the amount of sharing and re-using of needles. Their study did not offer insights into the degree to which individuals switched from injection to non-injection forms of use because of difficulties injecting BTH. However, their study does raise important questions regarding the role of purity, concentration, and morphology in understanding the complex role of consumption practices, addiction severity, and treatment needs.

One of the most striking demographic findings was that people living in rural areas had higher odds of injection route of administration. However, careful inspection of this finding reveals that the largest proportion of illicit drug users remains concentrated in urban areas, where approximately 95% of the approximately 6.6 million past-year users of heroin, methamphetamine, or cocaine reside (SAMHSA, 2008). A higher percentage of the IDU population is likely to be found in metropolitan areas, though a much larger percentage of those users engage in non-injectable forms of use compared to those living in rural areas. Based on our findings, IDUs in rural areas may represent a ‘hidden epidemic’ in need of further study because a significant body of work among IDUs has largely focused on urban areas (Brady et al., 2008).

A key limitation to keep in mind when evaluating results from this paper is that NSDUH excludes institutionalized populations (e.g., military personnel residing on government installations, prisoners, hospital inpatients). One excluded subgroup of particular relevance to this study involves clients receiving inpatient substance abuse treatment, either detoxification services or inpatient residential treatment. This is a relatively small and unique population where clients live in highly monitored environments, which limit their opportunities to use drugs and alcohol. Detoxification is restricted to several days and inpatient substance abuse treatment ranges between 30 and 90 days (Simpson, Hubbard, et al., 2000). Therefore, NSDUH captures these types of individuals after they are discharged from care, thus enabling characterization of their substance use patterns after institutionalization. The NSDUH recently changed from a household (i.e., address-based) design to one that seeks to include high-risk populations through segmented sampling

procedures. To date, there are no studies that have compared the sampling properties between NSDUH and hard-to-reach populations that are traditionally recruited via targeted sampling or respondent driven sampling. The current work provides an important complement to significant community-based designs that study the complexities of injection drug use.

Mindful of these limitations, results from this cross sectional study provides critical information on differences in demographic and risk factor profiles of people who use different routes of administration to consume illicit drugs. While clinical intuition or anecdotal case studies among treatment providers confirms that there are difference in the types of clients based on the route of administration and choice of drug abuse. The current study offers scientific confirmation of these hypotheses. This work may also inform future research that utilizes prospective longitudinal designs to examine the developmental sequencing of the psychosocial factors (e.g., physical health, major depressive episodes), poly-drug use, and treatment utilization. These studies may also highlight salient prevention and treatment points in the usage trajectory that may be used to alter the developmental course from initiation of first illicit use, moderate levels of use to more harmful levels of use, or transitions from regular use to usage patterns involving injection forms of self-administration.

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Table 1

Demographic Characteristics of Heroin, Methamphetamine, and Cocaine Users in Past Year: 2005–2007 NSDUH

	IDU[a] n=396[b]; 0.17%[b,c] (0.02)[b]	Non-IDU[a] n=6,023[b]; 2.52%[b,c] (0.05)[b]	IDU versus Non-IDU Routes of Administration[a](ref)					
Demographic Characteristic	%[b,d] (se)[b]	%[b,d] (se)[b]	OR[b]	95% CI[b]	P[b]	AOR[b]	95% CI[b]	P[b]
SEX								
Male	6.8 (0.8)	93.2 (0.8)	1.18	(0.83–1.67)	.342	1.18	(0.83–1.69)	.340
Female	5.8 (0.8)	94.2 (0.8)	1.00			1.00		
RACE								
White, non-Hispanic	6.9 (0.7)	93.1 (0.7)	1.00			1.00		
Black, non-Hispanic	4.9 (2.3)	95.1 (2.3)	0.69	(0.25–1.85)	.457	0.41	(0.17–0.99)	**.049**
Hispanic	6.4 (2.2)	93.6 (2.3)	0.92	(0.40–2.12)	.853	0.97	(0.42–2.24)	.952
Other race	3.5 (1.0)	96.5 (1.0)	0.49	(0.26–0.93)	**.031**	0.49	(0.25–0.94)	**.033**
AGE								
12–17	3.8 (2.5)	96.2 (2.5)	0.74	(0.47–1.15)	.183	0.59	(0.23–1.46)	.250
18–25	5.0 (0.4)	95.0 (0.4)	1.00			1.00		
25–34	7.3 (1.1)	92.7 (1.1)	1.48	(1.01–2.17)	**.044**	1.82	(1.22–2.71)	**.003**
35 or older	8.1 (1.5)	91.9 (1.5)	1.67	(1.10–2.54)	**.016**	1.66	(0.92–3.01)	.087
MARITAL (age 18+)								
Married/Living as married	5.3 (1.1)	94.7 (1.1)	0.86	(0.53–1.14)	.556	0.71	(0.37–1.44)	.288
Never married	6.1 (1.1)	93.9 (1.1)	1.00			1.00		
Divorced/separated/widowed	9.8 (2.0)	90.2 (2.0)	1.68	(1.11–2.81)	**.035**	1.09	(0.54–2.18)	.799
EMPLOYMENT (age 15–65)								
Full time	4.3 (0.5)	95.7 (0.5)	0.39	(0.26–0.58)	**<.001**	0.36	(0.23–0.55)	**<.001**
Part time	5.5 (1.3)	94.5 (1.3)	0.50	(0.29–0.86)	**.014**	0.57	(0.33–0.98)	**.043**
Unemployed	10.3 (1.5)	89.7 (1.5)	1.00			1.00		
EDUCATION (age 18+)								
Less than High School	10.2 (1.7)	89.8 (1.7)	1.00			1.00		
High school graduate/GED	6.9 (1.0)	93.1 (1.0)	0.65	(0.40–1.04)	.077	0.75	(0.46–1.20)	.229
Some college/tech/college grad	5.0 (0.8)	95.0 (0.8)	0.30	(0.30–0.71)	**<.001**	0.53	(0.33–0.83)	**.006**
VETERAN (age 18+)								

Demographic Characteristic	IDU[a] n=396[b]; 0.17%[b,c] (0.02)[b] %[b,d] (se)[b]	Non-IDU[a] n=6,023[b]; 2.52%[b,c] (0.05)[b] %[b,d] (se)[b]	IDU versus Non-IDU Routes of Administration[a](ref) OR[b]	95% CI[b]	P[b]	AOR[b]	95% CI[b]	P[b]
Yes	10.8 (3.4)	89.2 (3.4)	1.00			1.00		
No	6.3 (0.6)	93.7 (0.6)	0.56	(0.27–1.13)	.107	0.63	(0.31–1.27)	.200
METROPOLITAN								
Large Metro (?1 million)	5.9 (0.9)	94.1 (0.9)	0.35	(0.21–0.58)	**<.001**	0.43	(0.21–0.71)	**<.001**
Small Metro (<1 million)	6.2 (0.7)	93.8 (0.7)	0.37	(0.24–0.57)	**<.001**	0.43	(0.26–0.71)	**<.001**
Rural	15.1 (2.4)	84.9 (2.4)	1.00			1.00		

Notes: n=unweighted sample combined 2005–2007, se=standard error, OR=unadjusted odds ration, AOR=adjusted odds ratio controlling for listed variables. CI=confidence interval, P=P-value, STD=sexually transmitted disease, ref=reference category (1.00). P<.05 in **BOLD**

[a] IDU=Injection use of heroin, methamphetamine, or cocaine; Other routes of administration include snorting and swallowing.

[b] Unweighted cell n presented, estimates (% and SE) and test statistics (chi-square, P-values) adjusted using SUDAAN to accommodate design effect.

[c] Estimate percentaged among total population aged 12 or older.

[d] Estimate retricted to past year illicit users of heroin, methamphetamine, cocaine and percentaged by demographic characteristics.

Table 2

Substance Use, Mental and Physical Health Characteristics by IDU and Non-IDUs in Past Year: 2005–2007 NSDUH

	Heroin/Meth/Cocaine n=6,419; 2.07%[b] (0.05)[b]				Heroin n=459; 0.19%[b] (0.02)[b] of Total Pop.			
	IDU[a] n=396[b]	Non-IDU[a] n=6,023[b]			IDU[a] n=203[b]	Non-IDU[a] n=256[b]		
	0.17%[b,c] (0.02)[b]	2.52%[b,c] (0.01)[b]			0.09%[b,c] (0.01)[b]	0.09%[b,c] (0.01)[b]		
Substance Use Characteristic	%[b,d] (se)[b]	%[b,d] (se)[b]	χ^2	P[b]	%[b,d] (se)[b]	%[b,d] (se)[b]	χ^2	P[b]
GENERAL HEALTH								
Excellent/very good/good	79.1 (3.2)	86.6 (0.8)	4.9	**.030**	82.7 (4.9)	79.4 (5.4)	0.2	.642
Fair/poor	20.9 (3.2)	13.4 (0.8)			17.3 (4.9)	20.6 (5.4)		
MAJOR DEPRESSIVE EPISODE, PY	25.8 (3.6)	17.9 (0.8)	4.6	**.036**	18.2 (5.8)	18.1 (3.7)	0.1	.992
ABUSE/DEPENDENCE[e]	59.5 (4.3)	27.0 (1.2)	41.1	**<.001**	67.7 (5.4)	38.2 (5.6)	9.8	**.003**
RECEIVED TREATMENT, PY	42.0 (4.1)	11.5 (0.8)	39.3	**<.001**	55.8 (5.8)	28.5 (4.6)	14.5	**.003**
PERCEIVED NEED FOR TREATMENT	18.7 (3.6)	6.6 (0.7)	10.5	**.001**	16.7 (4.2)	10.6 (3.5)	1.3	.260
UNMET NEED FOR TREATMENT[f]	47.3 (5.6)	75.2 (0.7)	23.5	**<.001**	38.6 (7.1)	44.1 (8.7)	0.3	.607
ALCOHOL ABUSE/DEPENDENCE	43.6 (4.6)	43.8 (1.1)	0.1	.960	49.9 (6.6)	44.8 (4.9)	0.4	.555
OTHER ILLICIT ABUSE/DEPENDENCE	44.0 (4.7)	24.4 (0.6)	23.5	**<.001**	42.7 (6.2)	42.7 (6.2)	0.1	.946
STD, PY	11.2 (3.6)	8.3 (0.6)	0.6	.446	7.9 (5.1)	3.1 (0.8)	0.9	.352
ARRESTED/BOOKED, PY	49.6 (4.2)	19.4 (0.7)	37.4	**<.001**	57.8 (6.3)	49.1 (6.4)	0.7	.407

	Methamphetame n=1,319; 0.56%[b] (0.03)[b]				Cocaine n=5,684; 2.36%[b] (0.05)[b]			
	IDU[a] n=186[b]	Non-IDU[a] n=1,133[b]			IDU[a] n=162[b]	Non-IDU[a] n=5,522[b]		
	0.07%[b,c] (0.01)[b]	0.48%[b,c] (0.07)[b]			0.07%[b,c] (0.02)[b]	2.29%[b,c] (0.05)[b]		
Substance Use Characteristic	%[b,d] (se)[b]	%[b,d] (se)[b]	χ^2	P[b]	%[b,d] (se)[b]	%[b,d] (se)[b]	χ^2	P[b]
GENERAL HEALTH								
Excellent/very good/good	13.9 (4.9)	86.1 (2.2)	1.9	.175	76.2 (4.8)	86.5 (0.9)	5.3	**.025**

	Methamphetame n=1,319; 0.56%[b] (0.03)[b]				Cocaine n=5,684; 2.36%[b] (0.05)[b]			
	IDU[a] n=186[b] 0.07%[b,c] (0.01)[b]	Non-IDU[a] n=1,133[b] 0.48%[b,c] (0.07)[b]			IDU[a] n=162[b] 0.07%[b,c] (0.02)[b]	Non-IDU[a] n=5,522[b] 2.29%[b,c] (0.05)[b]		
Substance Use Characteristic	**%[b,d] (se)[b]**	**%[b,d] (se)[b]**	**χ^2**	**P[b]**	**%[b,d] (se)[b]**	**%[b,d] (se)[b]**	**χ^2**	**P[b]**
Fair/poor	21.1 (4.9)	13.9 (2.2)			23.8 (4.8)	13.5 (0.9)		
MAJOR DEPRESSIVE EPISODE, PY	32.3 (4.6)	23.1 (2.2)	3.2	.080	33.7 (5.8)	17.4 (0.9)	5.6	**.020**
ABUSE/DEPENDENCE[e]	26.8 (5.9)	16.5 (1.5)	3.1	.080	53.5 (5.6)	27.0 (1.3)	12.4	**<.001**
RECEIVED TREATMENT, PY	34.5 (5.1)	14.3 (1.7)	18.4	**<.001**	51.3 (6.3)	11.7 (0.9)	18.8	**<.001**
PERCEIVED NEED FOR TREATMENT	73.3 (6.5)	7.4 (1.6)	6.9	**.011**	23.0 (5.9)	7.0 (0.8)	7.5	**.008**
UNMET NEED FOR TREATMENT[f]	46.6 (11.3)	74.0 (5.5)	3.6	.069	27.4 (7.0)	75.6 (2.1)	11.3	**.001**
ALCOHOL ABUSE/DEPENDENCE	32.5 (5.6)	37.6 (3.1)	0.7	.406	47.2 (7.2)	45.7 (1.1)	0.1	.832
OTHER ILLICIT ABUSE/DEPENDENCE	48.8 (6.7)	27.6 (1.8)	9.9	**.002**	48.3 (6.9)	25.3 (0.7)	12.0	**.001**
STD, PY	13.8 (5.0)	9.8 (1.5)	0.6	.455	7.5 (3.0)	8.2 (0.7)	0.1	.803
ARRESTED/BOOKED, PY	43.1 (6.8)	16.1 (1.9)	8.6	**.004**	57.7 (5.9)	19.5 (0.7)	19.7	**<.001**

Notes: n=unweighted sample combined 2005–2007, se=standard error, IDU=injection use of heroin, methamphetamine, or cocaine. P=P-value, PY=past year, STD=sexually transmitted disease. **P<.05 in BOLD**.

[a] IDU=Injection use of heroin, methamphetamine, or cocaine; Other routes of administration include snorting and swallowing.

[b] Unweighted cell n presented, estimates (% and SE) and test statistics (chi-square, P-values) adjusted using SUDAAN.

[c] Estimate percentaged among total population aged 12 or older.

[d] Estimate retricted to past year illicit users of heroin, methamphetamine, cocaine and percentaged by route of adminstration.

[e] Defined by DSM-IV abuse/dependence for drug listed in column.

[f] Unmet need defined by (a) DSM-IV abuse/dependence and/or (b) perceived need for treatment but did not receive treatment.

[g] Includes marijuna, inhalents, hallucinogens, prescription pain relievers, tranquilizers, and sedatives.

Table 3

Summary Table Comparing Effect Sizes of Significant Differences among IDUs and Non-IDUs

Substance Use Characteristic	IDU % (SE)	Non-IDU % (SE)	Cohen's *d*
GENERAL HEALTH (FAIR/POOR)	20.9 (3.2)	13.4 (0.8)	2.3
MAJOR DEPRESSIVE EPISODE, PY	25.8 (3.6)	17.9 (0.8)	2.2
ABUSE/DEPENDENCE	59.5 (4.3)	27.0 (1.2)	7.6
RECEIVED TREATMENT, PY	42.0 (4.1)	11.5 (0.8)	7.4
PERCEIVED NEED FOR TREATMENT, PY	18.7 (3.6)	6.6 (0.7)	3.4
UNMET NEED FOR TREATMENT	47.3 (5.6)	75.2 (0.7)	4.9
OTHER ILLICIT ABUSE/DEPENDENCE	44.0 (4.7)	24.4 (0.6)	4.2
ARRESTED/BOOKED, PY	49.6 (4.2)	19.4 (0.7)	7.2

Note: Percentages and standard errors (SE) computed via SUDAAN to account for design effect.

PY=Past year. Cohen's *d* (Cohen, 1988) adjusted for sampling weights and variance.